I. Claims 1 - 16, 18, 24-28 (part of each), and 29 drawn to compounds of formula I with A as **pyrimidine**, or formulae IIa and IIc, classified in class 544, subclasses 326, 328, 329.

II. Claims 1 - 11, 18, 24 (part of each), drawn to compounds of formula I with A as **pyridazine**, or formula IIb, classified in class 544, subclass 238.

III. Claims 1 - 16, 18, 24-28 (part of each) drawn to compounds of formula I with A as **pyrazine**, or formula IId, classified in class 544, subclass 365.

IV. Claims 1 - 16, 18, 24-28 (part of each), and 29 drawn to compounds of formula I with A as **1,2,5-thiadiazole**, or formula IIe, classified in class 548, subclass 134.

V. Claims 1 - 16, 18, 24-28 (part of each), and 29 drawn to compounds of formula I with A as a ring other than those mentioned in Groups I-IV, classified in classes 540, 544, 546, 548, 549, 558, 560, etc., various subclasses.

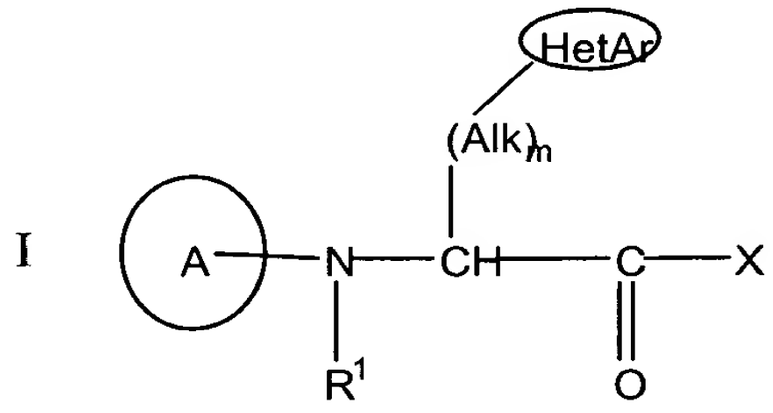
VI. Claims 17, and 19-23 (part of each), and 29 drawn to method of treating a disease mediated by VLA-4, classified in class 514, various subclasses.

2. Groups I-V

Applicants hereby elect Group I with traverse.

The restriction requirement is traversed for the following reasons. The present invention is based on the discovery that the presence of a nitrogen containing heteroaryl group at the terminal position of the certain alanine derivatives provides significant advantages vis-a-vis aryl or other heteroaryl groups at this position in the molecule. (Specification, page 5, lines 10-21).

Accordingly, Applicants claim compounds of formula I:



I

wherein:

A is an aryl, heteroaryl, cycloalkyl, or heterocyclic group wherein said aryl, heteroaryl, cycloalkyl, or heterocyclic group is optionally substituted, on any ring atom capable of substitution, with 1-3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, substituted amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, oxo, carboxyl, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where each R is independently hydrogen or alkyl,$-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl,$-N[S(O)_2-NR']_2$ where each R′ is independently selected from the group consisting of

alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

HetAr is a nitrogen containing heteroaryl or a nitrogen containing substituted heteroaryl group;

Alk is an alkylene group of 1 to 4 carbons;

m is 0 or 1;

R^1 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

X is selected from the group consisting of hydroxyl, alkoxy, substituted alkoxy, alkenoxy, substituted alkenoxy, cycloalkoxy, substituted cycloalkoxy, cycloalkenoxy, substituted cycloalkenoxy, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy and -NR″R″ where each R″ is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

and enantiomers, diastereomers and pharmaceutically acceptable salts thereof;

and further wherein the compound of Formula (I) has a binding affinity to VLA-4 as expressed by an IC_{50} of about 15μM or less.

Given the fact that all claimed compounds represent these certain 3-(heteroaryl) alanine derivatives, Applicants submit that the compounds of Groups I-V are so closely related, that a search and examination of the entire claim can be made without serious burden. The compounds of Groups I-V differ only in the *A* substituents at nitrogen of α-amino group of these 3-(heteroaryl) alanine derivatives. Applicants note that a proper search of the compound would, by necessity, require a proper search of all *A* substituents as presently defined. Thus, Applicants submit that the entire group as presently claimed can be searched simultaneously, and that a duplicative search, with possibly inconsistent results,

may occur if the restriction requirement is maintained. Accordingly, this also renders the restriction requirement as improper. See MPEP §803.

In addition it is submitted that this restriction is inconsistent with *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) in which the court articulated the general proposition that:

> [A]n applicant has a right to have *each* claim examined on the merits. If an applicant submits a number of claims, it may well be that pursuant to a proper restriction requirement, those claims will be dispersed to a number of applications. Such action would not affect the right of the applicant eventually to have each of the claims examined in the form he considers to best define his invention. If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the subgenera would be defined by the examiner rather than by the applicant, it is not inconceivable that a number of the fragments would not be described in the specification. *Id.* at 331. (Emphasis in original).

In light of the above, Applicants submit that Groups I-V should be combined.

3. Groups I-V and Group VI

The outstanding Office Action indicates that inventions of Groups I-V and Group VI are related as product and process of use and requires election of invention of Groups I-V or Group VI.

In response, Applicants elect Group I with traverse. Applicants respectfully traverse this requirement for restriction as it relates to the process and product claims for the following reasons.

An application may properly be restricted to one of two or more claimed inventions if (a) the inventions are independent or distinct as claimed; and (b) a serious burden is

imposed on the Examiner if restriction is not required. If the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to independent or distinct inventions. See MPEP § 803.

In the present case, the Examiner has indicated that restriction of the process and product claims is required because these inventions are distinct. Applicants submit that it is neither proper nor necessary to separate these inventions because even they are distinct, an undue burden would not be imposed on the Examiner if these groups were examined together because pertinent art relating to the claimed products is also likely to relate to the methods of using them.

Specifically, the background in Applicants specification beginning on page 1 describes the interrelationship between desirability of providing new compounds which bind to VLA-4 for using them as inhibitors of adhesion in the treatment of inflammatory brain diseases and other inflammatory conditions.

Accordingly, a combined search and examination of the subject matter of Claims 1-29 should not impose an undue burden on the Examiner since any document disclosing compounds of formula I, is also likely to disclose or be relevant to the methods of using these compounds. Thus, Applicants respectfully request that the requirement that the products of Group I-V and the processes of Group VI be restricted to separate groups be withdrawn.

In view of the above remarks, withdrawal of the requirement for restriction and examination of this application on the merits is earnestly solicited.

If the Examiner has any questions concerning the response or the application in general, the Examiner is invited to contact the undersigned so as to expedite prosecution.

Respectfully submitted,
BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: April 28, 2003

By: Galina Yakovleva
Galina M. Yakovleva
Registration No. 47,192

Post Office Box 1404
Alexandria, Virginia 22313-1404
(650) 622-2300